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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,472	07/18/2003	Erik Hendrikus, G., M. Boddeke	2183-6042US	4438

24247 7590 01/13/2006

TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,472	BODDEKE ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11,12,14-16,18 and 19* is/are pending in the application.

4a) Of the above claim(s) *11,12 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-8,11,12,14-16,18 and 19* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 3 November 2005 have been entered. Claims 9, 10, 13, and 17 are canceled; claims 18 and 19 are new. Claims 1 – 8, 11 – 12, 14 – 16, and 18 – 19 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Claims 11 – 12 and 14 – 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 25 April 2005.

4. Claims 1 – 8 and 18 – 19 are under examination.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The European application 01200181.4, filed 18 January 2001, and submitted to the USPTO on 17 October 2005, has been received.

Withdrawn Rejections and Objections

6. The following rejections and objections made in the previous office action are withdrawn:

1) The objection to the specification is withdrawn in light of the amendment.

2) The objections to claims 9 – 10 and 13 are moot; the claims have been canceled.

3) The objections to claims 3 – 7 are withdrawn in light of the amendments.

4) The rejection of claims 1 – 8 under 35 USC 112, first paragraph for lacking written description is withdrawn. The amendments are sufficient to overcome the rejections; claims 9 – 10, 13 and 17 are canceled rendering the rejections moot.

5) The rejections of claims 1 – 8 under 35 USC 112, second paragraph for lacking written description are withdrawn. The amendments are sufficient to overcome the rejections; claims 9 – 10, 13 and 17 are canceled rendering the rejections moot.

6) The rejection of claims 1,2, 8, and 13 under 35 USC 102(b). Boddeke teaches calcium transients, not calcium gradients as claimed herein.

Rejections Maintained and Necessitated by Amendment

Claim Objections

7. Claims 6 and 19 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 6 and 19 each recite the limitation "wherein the cell which expresses the chemokine receptor is a cultured cell." However claims 1 and 2, from which 6 and 19 depend respectively, are limited to *in vitro* methods. Alberts et al. (1994. Molecular Biology of the Cell, pp. 158 – 159) teach that *in vitro* methods are those that use cultured cells. Thus as the methods must be performed on cultured cells, claims 6 and 19 do not reasonably limit claims 1 and 2.

Claim Rejections - 35 USC § 112

8. Claims 1 – 8 and 18 – 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for contacting a cell with a candidate compound and measuring the chemotaxis of the cell or the intracellular calcium gradients, does not reasonably provide enablement for the detection of agonists of CCR12, or for identification of agents for treatment of any disease or condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are very broad in that the methods will permit identification of all chemotactic agents, whether or not those agents operate through CCR12. There is no requirement for any controls in the claimed methods, and thus addition of any agent which either induces a calcium gradient or chemotaxis will result in that agent being identified as a chemokine receptor agonist. Clearly not all agents that would turn up "positive" in the assays, or even a reasonable number of members of this very broad genus, are actually chemokine receptor agonists. For example, Alberts et al. (1994. Molecular Biology of the Cell, pp. 831 – 832) teaches that addition of cyclic AMP to medium comprising *Dictyostelium discoideum* results in chemotaxis. However there is no indication that cAMP is a chemokine agonist. While this example clearly is not prior art as the *Dictyostelium discoideum* organisms do not express CCR12, it is on point as it indicates that many agents will be falsely identified as chemokine agonists. As no controls are required in the

claimed methods, the artisan would identify as a chemokine agonist any molecule which induces chemotaxis, whether or not CCR12 is required for said chemotaxis.

Additionally, the claims require the skilled artisan to identify as a chemokine agonist any substance after intracellular calcium gradients are measured. The claims do no require that a particular gradient be present, that it be induced by the test compound, or that CCR12 mediates the presence or absence of the gradient. Thus if the artisan added SLC or Fractalkine to the cell culture, which the specification discloses have no chemotactic effect on CCR12-expressing cells (see p. 23), and then measured the intracellular calcium gradient, the claims require that these agents be identified as agonists.

In the remarks filed 3 November 2005, applicant argues that the amended claims are fully enabled because they identify agonists/antagonists of the receptors which may be of therapeutic use (see p. 8, first complete paragraph). Applicant's arguments have been fully considered but are not persuasive. First, the methods do not identify agonists/antagonists of the CCR12 receptor. The preambles are drawn to methods of detecting agonists; antagonists are not mentioned. Second, as set forth above, the claims do not require any controls and thus will identify all chemoattracting molecules, whether or not they operate through CCR12, and also identify all molecules whenever intracellular calcium is measured. Third, even if the claims were limited to identification of CCR12 agonists, it is not immediately clear why the artisan would want to perform the assay. The specification discloses that MCP-1 is chemoattractive to cells expressing CCR12. However MCP-1 is well-known to play an important role in increasing the severity of many inflammatory conditions. MacDermott (1999. Journal of Clinical Immunology 19:266-272) teaches that MCP-1 and other chemokines are known to play pathogenic roles in the development of inflammatory bowel disease, and that novel therapeutic approaches should attempt to inhibit rather than serve as agonists of chemokines. Since chemokine agonists will exacerbate disease, it is not immediately apparent what the artisan will do with the compounds identified as agonists by the assays.

9. Claims 1 – 8 and 18 – 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1 and 2, from which all other claims depend, recite the limitation "measuring intracellular calcium gradients". The examiner is able to find support for intracellular calcium transients, for example on p. 19 paragraph 0057, but is unable to find support for the measurement of calcium gradients. These are different terms; a gradient is a change in concentration across space, whereas a transient is a brief current.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1 – 4, 6 – 7, and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Schweickart (Journal of Biological Chemistry 275:9550-9556). In the previous office action this rejection was made under § 102(b). However as the foreign priority documents have been filed and constitute an enabling disclosure, the effective filing date has changed; thus Schweickart qualifies under § 102(a).

Schweickart et al. teach screening 29 cytokines for their ability to induce chemotaxis in cells expressing CCR11 (see p. 9552, top of second column). The specification teaches that CCR11 is a synonym for L-CCR (see page 4 line 4 and page 9 line 8). Schweickart et al. teach comparing the ability of candidate compounds to mimic the effects of MCP-1 in the chemotaxis assay (see figure 5, for example), thereby fairly meeting the limitations of "checking" and "determining" recited in claims 1 and 2. As claims 6 and 19 do not limit claims 1 and 2, they also stand rejected. Schweickart teaches comparing the ability of several compounds to that of MCP-1, MCP-2, MCP-3, and RANTES (see Figures 5 and 6), meeting the limitations of claims 3 and 4. The cells used were transfected with nucleic acids encoding CCR11 (see p. 9551, first column, "CCR11 expression"), meeting the limitations of claim 7.

Applicant argues that Schweickart fails to meet the limitations of the amended claims as the subject matter of Schweickart is CCR11, whereas the claims are drawn to "a chemokine receptor known as CCR12". However applicant has clearly defined CCR11 to be synonymous and interchangeable with CCR11. See for example page 4 line 4 and page 9 line 8 of the specification. The term CCR12 has such breadth as to include CCR11, absent any recitation of

a sequence or other further identifying information. As applicant appears to believe that the two terms are interchangeable, Schweickart clearly anticipates the claimed invention.

12. Claims 1 – 4, 6 – 7, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Gray et al. (WO 01/66598, cited on IDS, published 13 September 2001, filed 5 March 2001, claiming priority to provisional applications filed 3 March 2000).

Gray teaches assays to detect modulators of CCR11 activity (see text beginning on p. 67 of Gray). The specification teaches that CCR11 is a synonym for L-CCR (see page 4 line 4 and page 9 line 8). Detailed instruction on how to measure intracellular calcium are provided by Gray beginning on p. 71, and chemotaxis assays are described on p. 75, which refers to text on pp. 60 – 62. On p. 61 lines 15 - 17, Gray teaches comparing the chemotactic effects of substances to those of the known chemoattractants MCP-1. As claims 6 and 19 do not limit claims 1 and 2, they also stand rejected. The cells used were transfected with nucleic acids encoding CCR11 (see p. 60, line 30 – 34) meeting the limitations of claim 7.

Applicant argues that Gray fails to meet the limitations of the amended claims as the subject matter of Gray is CCR11, whereas the claims are drawn to "a chemokine receptor known as CCR12". However applicant has clearly defined CCR11 to be synonymous and interchangeable with CCR11. See for example page 4 line 4 and page 9 line 8 of the specification. The term CCR12 has such breadth as to include CCR11, absent any recitation of a sequence or other further identifying information. As applicant appears to believe that the two terms are interchangeable, Gray clearly anticipates the claimed invention.

13. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Gish et al. (WO 98/01557, published 15 January 1998).

As set forth previously, Gish et al. teach SEQ ID NO:12; bases 85 – 1119 of their SEQ ID NO:12 are identical to applicant's SEQ ID NO:31, which is identified as human CCR12. Gish teaches a number of assays to determine the binding affinity and effects of compounds on this receptor. See for example pp. 46 – 47. Gish teaches how to perform screening assays with chemokines and with the chemokine receptors (see p. 43 – 46). The assays can use cells in culture (p. 47 lines 5 – 9). Gish teaches that compounds are screened and can be used in bioassays (see p. 42 line 31 – p. 43 line 5). Gish also teaches that cells can be used for the assays, and that they are particularly useful in assays which measure calcium gradients (see p. 45 lines 14 – 26). Thus Gish teaches each element of claims 1 and 6.

Applicant argues that Gish does not teach providing cells which express CCR12. Although Gish uses a different name, the sequence from Gish comprises a sequence that is identical to human CCR12. Gish teaches providing cells, and also teaches measuring calcium signals, as required in claim 1.

14. Claims 1 – 8 and 18 – 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Boddeke et al. (2000. Society for Neuroscience Abstracts 26(1 – 2):Abstract 726.13). Boddeke teaches contacting cells expressing inducible CCR ("CCRi") with MCP-1. While claim 1 is drawn to "CCR12", since the two inventors are both listed as authors on the reference by Boddeke, and because the specification teaches that CCR12 is also known as L-CCR, the teachings of Boddeke appear to be drawn to the same subject matter as that claimed herein, absent evidence to the contrary. Furthermore Shimada (1998. FEBS Letters 425:490-494) teaches that L-CCR is inducible, supporting the examiner's assertion that L-CCR is the same as CCRi. Boddeke teaches chemotaxis assays used for screening for agonists, meeting the limitation of claim 1. Boddeke also anticipates claims 2 – 4, as the vehicle in which MCP-1 was dissolved can be deemed a "candidate drug compound". Boddeke teaches that LPS induces CCRi, meeting the limitation of claims 5 and 18. As claims 6 and 19 do not limit claims 1 and 2 respectively, they are also rejected. Claims 7 – 8 are rejected as Boddeke teaches CCRi nucleic acid transfected into HEK cells are suitable for the assay.

15. Claims 1 – 4, 6, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Peterson (1997. The Journal of Infectious Diseases 175:478 – 481).

Peterson teaches screening assays wherein cultured microglia and astrocytes are contacted with chemoattractant molecules, including MIP-1 alpha, MIP-1 beta, and MCP-1. Peterson also teaches comparing the chemoattractive abilities of these molecules with one another (see p. 480, first complete paragraph). The specification provides evidence that both astrocytes and microglia express CCR12 (p. 6, paragraph 0011 for example). Thus the reference fairly anticipates claims 1 – 4. Claims 6 and 19 do not limit claims 1 and 2 respectively, so they are also rejected.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Schweickart, Gray, Gish, or Peterson, each in view of Shimada (1998. FEBS Letters 425:490-494). The reasons why Schweickart, Gray, Gish, and Peterson each anticipate claim 1 are provided above in the rejections under 35 USC 102. None of Schweickart, Gray, Gish, or Peterson teach adding LPS to increase the expression of CCR12.

Shimada teaches that adding LPS is sufficient to increase expression of L-CCR (see Figure 1, for example). The specification discloses that this is another name for CCR12. It would have been obvious to one of ordinary skill in the art to add LPS to the screening assays, as taught by Shimada, with a reasonable expectation of success. The motivation to do so would be to increase the amount of chemokine receptor present, thereby augmenting the signals transduced by the receptor.

18. Claims 2 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Schweickart, Gray, or Peterson, each in view of Shimada. The reasons why Schweickart, Gray, and Peterson each anticipate claim 2 are provided above in the rejections under 35 USC 102. None of Schweickart, Gray, Gish, or Peterson teach adding LPS to increase the expression of CCR12.

Shimada teaches that adding LPS is sufficient to increase expression of L-CCR (see Figure 1, for example). The specification discloses that this is another name for CCR12. It would have been obvious to one of ordinary skill in the art to add LPS to the screening assays, as taught by Shimada, with a reasonable expectation of success. The motivation to do so would be to increase the amount of chemokine receptor present, thereby augmenting the signals transduced by the receptor.

19. Claims 1, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schweickart, Gray, Gish, or Peterson, each in view of Sullivan (1999. Biochemical and Biophysical Research Communications 263:685 – 690). The reasons why Schweickart, Gray, Gish, and Peterson each anticipate claim 1 are provided above in the rejections under 35 USC 102. None of Schweickart, Gray, Gish, or Peterson teach using transected cells generally or HEK cells in particular for the screening assays.

Sullivan teaches chemotaxis assays using chemokine receptors stably transfected in HEK-293E cells. Sullivan teaches that the method is advantageous over other methods, as it

allows for high expression of the receptor and a more accurate calculation of ligand binding affinity and kinetics (see p. 689, first complete paragraph). Furthermore Sullivan teaches that understanding these parameters is crucial if the molecules which bind to the receptor are to be developed as drugs (see p. 688, final paragraph). It would have been obvious to one of ordinary skill in the art to perform the screening assays from any of Schweickart, Gray, Gish, or Peterson by transfecting the nucleic acid encoding the receptor into HEK cells, with a reasonable expectation of success. The motivation to do so would be to take advantage of this system, which allows for more accurate calculation of pharmacologically significant parameters.

Conclusion

20. No claim is allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
January 4, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER
1-10-05